GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Tenth Edition

McGraw-Hill
MEDICAL PUBLISHING DIVISION

New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

EDITORS

Joel G. Hardman, Ph.D.

Professor of Pharmacology, Emeritus
Vanderbilt University Medical Center
Nashville, Tennessee

Lee E. Limbird, Ph.D.

Professor of Pharmacology
Associate Vice Chancellor for Research
Vanderbilt University Medical Center
Nashville, Tennessee

CONSULTING EDITOR

Alfred Goodman Gilman, M.D., Ph.D., D.Sc. (Hon.)

Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology
Regental Professor and Chairman, Department of Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas

McGraw-Hill
A Division of The McGraw-Hill Companies

Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10/e

1234567890 DOWDOW 0987654321

ISBN 0-07-135469-7

This book was set in Times Roman by York Graphic Services, Inc. The editors were Martin J. Wonsiewicz and John M. Morriss; the production supervisor was Philip Galea; and the cover designer was Marsha Cohen/Parallelogram. The index was prepared by Irving Condé Tullar and Coughlin Indexing Services, Inc.
R.R. Donnelley and Sons Company was printer and binder.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Goodman and Gilman's the pharmacological basis of therapeutics.—10th ed. / [edited by]
Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-07-135469-7
1. Pharmacology. 2. Chemotherapy. I. Title: Pharmacological basis of therapeutics.
II. Goodman, Louis Sanford III. Gilman, Alfred IV. Hardman, Joel G.
V. Limbird, Lee E. VI. Gilman, Alfred Goodman
[DNLM: 1. Pharmacology. 2. Drug Therapy. QV 4 G6532 2002]
RM300 G644 2001
615'.7—dc21 2001030728

INTERNATIONAL EDITION ISBN 0-07-112432-2

Peak concentrations in plasma are reached within 1 to 2 hours and then decline with an apparent half-life of approximately 3 hours; this value does not change with long-term use. Naltrexone is metabolized to 6-naltrexol, which is a weaker antagonist but has a longer half-life of about 13 hours. Naltrexone is much more potent than naloxone, and 100-mg oral doses given to patients addicted to opioids produce concentrations in tissues sufficient to block the euphorigenic effects of 25-mg intravenous doses of heroin for 48 hours (*see* Gonzalez and Brogden, 1988).

Therapeutic Uses

Opioid antagonists have established uses in the treatment of opioid-induced toxicity, especially respiratory depression; in the diagnosis of physical dependence on opioids; and as therapeutic agents in the treatment of compulsive users of opioids, as discussed in Chapter 24. Their potential utility in the treatment of shock, stroke, spinal cord and brain trauma, and other disorders that may involve mobilization of endogenous opioid peptides remains to be established. *Naltrexone* is approved by the United States Food and Drug Administration for treatment of alcoholism (*see* Chapters 18 and 24).

Treatment of Opioid Overdosage. *Naloxone hydrochloride* is used to treat opioid overdose. As discussed earlier, it acts rapidly to reverse the respiratory depression associated with high doses of opioids. However, it should be used cautiously, since it also can precipitate withdrawal in dependent subjects and cause undesirable cardiovascular side effects. By carefully titrating the dose of naloxone, it usually is possible to antagonize the respiratory-depressant actions without eliciting a full withdrawal syndrome. The duration of action of naloxone is relatively short, and it often must be given repeatedly or by continuous infusion. Opioid antagonists also have been effectively employed to decrease neonatal respiratory depression secondary to the intravenous or intramuscular administration of opioids to the mother. In the neonate, the initial dose is 10 μg/kg, given intravenously, intramuscularly, or subcutaneously.

CENTRALLY ACTIVE ANTITUSSIVE AGENTS

Cough is a useful physiological mechanism that serves to clear the respiratory passages of foreign material and excess secretions. It should not be suppressed indiscriminately. There are, however, many situations in which cough does not serve any useful purpose but may, instead, only annoy the patient or prevent rest and sleep. Chronic cough can contribute to fatigue, especially in elderly patients. In such situations the physician should use a drug that will reduce the frequency or intensity of the coughing. The cough reflex is complex, involving the central and peripheral nervous systems as well as the smooth muscle of the bronchial tree. It has been suggested that irritation of the bronchial mucosa causes bronchoconstriction, which, in turn, stimulates cough receptors (which probably represent a specialized type of stretch receptor) located in tracheobronchial passages. Afferent conduction from these receptors is *via* fibers in the vagus nerve; central components of the reflex probably involve several mechanisms or centers that are distinct from the mechanisms involved in the regulation of respiration.

The drugs that directly or indirectly can affect this complex mechanism are diverse. For example, cough may be the first or only symptom in bronchial asthma or allergy, and in such cases bronchodilators (*e.g.*, β_2-adrenergic receptor agonists; *see* Chapter 10) have been shown to reduce cough without having any significant central effects; other drugs act primarily on the central or the peripheral nervous system components of the cough reflex. The early literature on antitussives has been reviewed by Eddy *et al.* (1969).

A number of drugs are known to reduce cough as a result of their central actions, although the exact mechanisms are still not entirely clear. Included among them are the opioid analgesics discussed above (codeine and hydrocodone are the opioids most commonly used to suppress cough), as well as a number of nonopioid agents. Cough suppression often occurs with lower doses of opioids than those needed for analgesia. A 10- or 20-mg oral dose of codeine, although ineffective for analgesia, produces a demonstrable antitussive effect, and higher doses produce even more suppression of chronic cough.

In selecting a specific centrally active agent for a particular patient, the significant considerations are its antitussive efficacy against pathological cough and the incidence and type of side effects to be expected. In the majority of situations requiring a cough suppressant, liability for abuse need not be a major consideration. Most of the nonopioid agents now offered as antitussives are effective against cough induced by a variety of experimental techniques. However, the ability of these tests to predict clinical efficacy is limited.

Dextromethorphan. *Dextromethorphan* (*d*-3-methoxy-*N*-methylmorphinan) is the *d* isomer of the codeine analog methorphan; however, unlike the *l* isomer, it has no

analgesic or addictive properties and does not act through opioid receptors. The drug acts centrally to elevate the threshold for coughing. Its effectiveness in patients with pathological cough has been demonstrated in controlled studies; its potency is nearly equal to that of codeine. Compared with codeine, dextromethorphan produces fewer subjective and gastrointestinal side effects (Matthys *et al.*, 1983). In therapeutic dosages, the drug does not inhibit ciliary activity, and its antitussive effects persist for 5 to 6 hours. Its toxicity is low, but extremely high doses may produce CNS depression.

Sites that bind dextromethorphan with high affinity have been identified in membranes from various regions of the brain (Craviso and Musacchio, 1983). Although dextromethorphan is known to function as an NMDA-receptor antagonist, these binding sites are not limited to the known distribution of NMDA receptors (Elliott *et al.*, 1994). Thus, the mechanism by which dextromethorphan exerts its antitussive effects is still unclear. Two other known antitussives, carbetapentane and caramiphen, also bind avidly to this site, but codeine, levopropoxyphene, and other antitussive opioids (as well as naloxone) are not bound. Although noscapine (*see* below) enhances the affinity of dextromethorphan, it appears to interact with distinct binding sites (Karlsson *et al.*, 1988). The relationship of these binding sites to antitussive actions is not known; however, these observations, coupled with the ability of naloxone to antagonize the antitussive effects of codeine but not those of dextromethorphan, indicate that cough suppression can be achieved by a number of different mechanisms. The average adult dosage of *dextromethorphan hydrobromide* is 10 to 30 mg three to six times daily; however, as is the case with codeine, higher doses often are required. The drug is generally marketed for "over-the-counter" sale in numerous syrups and lozenges or in combinations with antihistamines and other agents.

Other Drugs. *Levopropoxyphene napsylate*, the *l*-isomer of dextropropoxyphene, in doses of 50 to 100 mg orally, appears to suppress cough to about the same degree as does 30 mg of dextromethorphan. Unlike dextropropoxyphene, levopropoxyphene has little or no analgesic activity.

Noscapine is a naturally occurring opium alkaloid of the benzylisoquinoline group; except for its antitussive effect, it has no significant actions on the CNS in doses within the therapeutic range. The drug is a potent releaser of histamine, and large doses cause bronchoconstriction and transient hypotension.

Other drugs that have been used as centrally acting antitussives include *carbetapentane, caramiphen, chlophedianol, diphenhydramine,* and *glaucine.* Each is a member of a distinct pharmacological class unrelated to the opioids. The mechanism of action of diphenhydramine, an antihistamine, is unclear. Although sedative effects are common, paradoxical excitement may be seen in infants; dryness of mucous membranes caused by anticholinergic effects and thickening of mucus may be a disadvantage. In general, the toxicity of these agents is low, but controlled clinical studies are still insufficient to determine whether or not they merit consideration as alternatives to more thoroughly studied agents.

Pholcodine [3-*O*-(2-morpholinoethyl)morphine] is used clinically in many countries outside the United States. Although structurally related to the opioids, it has no opioid-like actions because the substitution at the 3-position is not removed by metabolism. Pholcodine is at least as effective as codeine as an antitussive; it has a long half-life and can be given once or twice daily (*see* Findlay, 1988).

Benzonatate (TESSALON) is a long-chain polyglycol derivative chemically related to procaine and believed to exert its antitussive action on stretch or cough receptors in the lung, as well as by a central mechanism. It has been administered by all routes; the oral dosage is 100 mg three times daily, but higher doses have been used.

THERAPEUTIC USES OF OPIOID ANALGESICS

Sir William Osler called morphine "God's own medicine." Opioids are still the mainstay of pain treatment. However, the development of new analgesic compounds and new routes of administration have increased the therapeutic options available to clinicians, while at the same time helping to minimize undesirable side effects. In this section, we will outline guidelines for rational drug selection, discuss routes of administration other than the standard oral and parenteral methods, and outline general principles for the use of opioids in acute and chronic pain states.

Extensive efforts by many individuals and organizations have resulted in the publication of many useful guidelines for the administration of opioids. These have been developed for a number of clinical situations, including acute pain, trauma, cancer, nonmalignant chronic pain, and treatment of pain in children (Agency for Health Care Policy and Research, 1992a, 1992b, 1994; International Association for the Study of Pain, 1992; American Pain Society, 1999; Grossman *et al.*, 1999; World Health Organization, 1998; Berde *et al.*, 1990). These guidelines provide comprehensive discussions of dosing regimens and drug selection and also provide protocols for the management of complex conditions. In the case of cancer pain, adherence to standardized protocols for cancer pain management (Agency for Health Care Policy and Research, 1994) has been shown to improve pain management significantly (Du Pen *et al.*, 1999). Guidelines for the oral and parenteral dosing of commonly used opioids are presented in Table 23–6.

These guidelines are for acute pain management in opioid-naïve patients. Adjustments will need to be made for use in opioid-tolerant patients and in chronic pain states. For children under 6 months of age, especially those who are ill or premature, expert consultation should be obtained. The pharmacokinetics and potency of opioids